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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,841	02/14/2001	Merrill A. Biel	22,272-19	1618

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,841	BIEL, MERRILL A.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,10,12-15 and 45* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7,8,10,12-15 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-15, species administration of adjuvant after the administration of photodynamic light therapy, administration of an immune modulator after the administration of photodynamic light therapy, in Paper Nos. 6 and is acknowledged. In addition, in a telephonic interview with John Klos, on 11/20/02, the species administration of a photosensitizer agent proximate to the primary tumor site and the species intravenous administration of an adjuvant.

Applicant cancels claims 4, 9 and 11 and adds new claim 45, which is related to claims 1-15 and is not new matter.

Accordingly, claims 1-3, 5, 7-8, 10, 12-15, 45, species i.v. administration of an adjuvant(s) after the administration of photodynamic light therapy, administration of an immune modulator after the administration of photodynamic light therapy, and administration of a photosensitizer agent proximate to the primary tumor site are examined in the instant application. Claim 6 is withdrawn from consideration as being drawn to non-elected species.

PRIORITY DATE

The Examiner has established a priority date (02/14/01) for the instantly claimed application serial number 09/782841 as the application serial number 09/139861 to which priority is claimed does not recite the limitation of a method of treating a living body having a primary tumor and a metastatic tumor comprising administering an immunologic adjuvant, after administering photodynamic light therapy, and at a

standard concentration for immunization, wherein the administration of the adjuvant results in a systemic heightened nonspecific enhanced immune, and wherein the photodynamic light therapy (PDT) eradicates a primary tumor cells, releasing necrosis-related tumor cell specific antigens, and wherein as a result of an interaction between the increased level of nonspecific immune-related molecular and cellular factors and cells and the release of tumor cell specific antibodies, a systemic immunologic response is promoted and enhanced, yielding increased levels of tumor cell specific antibodies for eradicating cells of the metastatic tumor. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

REJECTION UNDER 35 USC 112 SECOND PARAGRAPH

1. Claims 1-3, 5, 7-8, 10, 12-15, 45 are indefinite because claims 1, 45 use of the language "proximate said primary tumor tissue site". Does Applicant mean "proximate to said primary tumor tissue site" ?

2. Claims 1-3, 5, 7-8, 10, 12-15, 45 are indefinite because it is not clear in claims 1, 45 what the claimed molecular and cellular factors and cells are.

3. Claims 1-3, 5, 7-8, 10, 12-15, 45 are indefinite because it is not clear in claims 1, 45 what "other" immunologic anti-tumor cell specific products and cells are.

4. Claims 1-3, 5, 7-8, 10, 12-15, 45 are indefnite because it is not clear in claims 1, 45 what "photodynamic light therapy released tumor cell specific antigens" are. Does

Applicant mean tumor cell specific antigens which are released from tumor cells treated with photodynamic light therapy?

5. Claims 1-3, 5, 7-8, 10, 12-15, 45 are indefnite because claims 1, 45 use the language "approximately". The term "approximately" in claims 1, 45 is a relative term which renders the claim indefinite. The term "approximately" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

6. Claims 1-3, 5, 7-8, 10, 12-15, 45 are indefinite, because in claims 1 and 45 it is not clear whether the light or the photosensitizing agent or both are administered proximate to the primary tumor site.

7. Claims 7 and 8 are indefinite for the use of the language "DETOX" which is a trademark.

REJECTION UNDER 35 USC 103

Claims 1-3, 5, 7-8, 10, 12-15, 45 are rejected under 35 USC 103 as being obviousness over Bellnier, DA, 1991, J Photochem. Photobiol, B:Biol, 8: 203-210, in view of US 4,96,3354, Krosl et al, 1996, Cancer Res, 56(14): 3281-6, Canti G et al, 1994, Anti-Cancer Drugs, 5: 443-447, Sakurai et al, 1989, Vaccine, 7(3): 269-74, Malik, A et al,1993, Infect Immunol, 61(12): 5062-6, Matsumoto, Y et al, 1991, Intl J Cancer, 49(3): 444-449, and Kim et al, 2000, Vaccine, 18: 597-603.

Claims 1-3, 5, 7-8, 10, 12-15, 45 are drawn to a method of treating a living body having a primary tumor and a metastatic tumor comprising administering intravenously an immunologic adjuvant, in one or more administrations after administering photodynamic light therapy proximate to the primary tumor site, and at a standard concentration for immunization, wherein the administration of the adjuvant results in a systemic heightened nonspecific enhanced immune, and wherein the photodynamic light therapy (PDT) eradicates a primary tumor cells, releasing necrosis-related tumor cell specific antigens. As a result of an interaction between the increased level of nonspecific immune-related molecular and cellular factors and cells and the release of tumor cell specific antibodies, a systemic immunologic response is promoted and enhanced, yielding increased levels of tumor cell specific antibodies for eradicating cells of the metastatic tumor. In addition to the adjuvant, an immune modulator is also administered after the administration of the photodynamic light therapy. The photosensitizing agent is administered intravenously. The light wavelength of the PDT ranges from about 400nm to about 800 nm, or from about 300 nm to about 700 nm, the light dosage of the PDT ranges from about 10 J/cm^2 to about 250 J/cm^2 and a light dosage rate ranges from about 50 mw/cm^2 to about 200 mw/cm^2. The adjuvant is DETOX which is administered at a 10% full strength concentration, at one or more separate administrations.

Due to the indefnite language of claims 1 and 45 and for the purpose of compact prosecution, it is assumed that the photosensitizing agent is administered proximate to the primary tumor site.

It is noted that compounds such as DETOX, GM-CSF and G-CSF are identified as adjuvants in the specification (p.6, second paragraph); and cytokines, including interleukins, TNF are identified as immune modulators (p.7, first paragraph), whereas it seems that TNF and cytokines are identified as adjuvants in the art (US 4,96,3354), since similar to other adjuvants, they induce cell-mediated immunity and antibody against antigens.

Bellnier et al teach that photodynamic therapy (PDT) of mice is potentiated by intravenous administration of tumor necrosis factor-alpha (TNF) before illumination (abstract and p. 205, last paragraph, bridging p. 206). Bellnier et al teach that PDT causes ischemic necrosis of tumor tissue (p.203). Bellnier et al further teach that TNF, given systemically or locally, has a multitude of effects, including neutrophil activation, production of prostaglandin E2, production of IL1 by monocytes and augmentation of natural killer cell activity, and may increase the likelihood of a complete tumor response from PDT (p. 204, first paragraph, and p.209, second paragraph). Bellnier et al also teach that a combination therapy is desirable to improve the therapeutic effect (p.204, second paragraph). Bellnier et al further teach that the light dose is standard, i.e.144 J cm^2 with 5 mg Photofrin II (i.p. injection), or 288 J cm^2 with 2.5 mg Photofrin II, the light is centered around 630 nm, and the dose rate is 160 mW cm^{-2}. Thus the light dose, wavelength, and the dose rate of the PDT are within the ranges of the claimed light dose, wavelength, and the dose rate of the PDT.

Bellnier et al do not teach treating metastatic tumors, wherein a photodynamic light therapy eradicates a primary tumor, and wherein the metastatic tumors are

specifically targeted by tumor specific antibodies derived from enhanced, systemic nonspecific immune response as a result of administration of an immunologic adjuvant and PDT. Bellnier et al do not teach administration of an adjuvant and an immune modulator after PDT administration. Bellnier et al do not teach administration of photosensitizing agent proximate to the primary tumor site.

US 4,963354 teaches that tumor necrosis factors (TNF), alone or together with cytokines such as IL-1 or INF-gamma, are capable of serving as non-toxic vaccine adjuvants, i.e. boosting cell-mediated immunity and induction of antibodies against antigens (abstract and examples 1 and 2).

Krosl et al teach peritumoral injection of GM-CSF, three times starting two days before a photodynamic therapy, and that GM-CSF treatment did increase the cytotoxic activity of tumor-associated macrophages against tumor cells. Krosl et al however teach that systemic treatment of high doses of GM-CSF may induce serious side effect, and i.v. injected GM-CSF has a relatively short half life.

Canti et al teach that PDT (photodynamic therapy) often incompletely destroy the neoplastic mass, and therefore it would be advantageous if the metastasized or undestroyed cancer cells could be eliminated immunologically rather than through chemotherapy (p.446, last paragraph). Canti et al also teach that PDT, besides killing neoplastic mass, is able to induce a strong specific anti-tumor immunity (p.446,second column).

Sakurai et al teach that monosaccharide-type adjuvant could be administered intravenously or intratumorally for treating lung metastasis.

Malik et al teach that the Freud complete adjuvant, and the DETOX adjuvant, when administered intravenously, are effective in the induction of cytotoxic T lymphocytes.

Matsumoto et al teach that granulocyte colony-stimulating factor (G-CSF), when administered intravenously, significantly inhibits lung and liver metastatasis, by activating neutrophils.

Kim et al teach that immunological adjuvants are important for induction of antibody and T-cells responses against tumor antigens (absract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine PDT with one or more immunologic adjuvants, such as TNF, IL-1, INF-gamma, monosaccharide-type adjuvant, Freud complete adjuvant, DETOX adjuvant, or G-CSF as taught by Bellnier et al, US 4,96,3354, Sakurai et al, Malik, A et al, Matsumoto, Y et al, and Kim et al for use in treating primary and metastatic tumors, as suggested by Canti et al, because a combination therapy is desirable to improve the therapeutic effect, as taught by Bellnier et al , and because TNF alone or together with other adjuvants are capable enhance cell-mediated immunity and produce antibody against antigen, as taught by US 4,963354, Malik, A et al, Matsumoto, Y et al, and Kim et al. It would have been obvious to administer the adjuvants intravenously, as taught by Bellnier et al, and in one or more administrations, because of the following reasons: 1) Different administration routes and times are routine in the art and would produce enhanced immune response, as taught by Bellnier et al, and Krosl et al, 2) Except GM-CSF, most adjuvants would be successful in

inducing an immune response when administered intravenously, as taught by Bellnier et al, Sakurai et al, Malik, A et al, Matsumoto, Y et al, and 3) For treating metastasis, a systemic immune response rather an immune response local to the primary tumor site would be favorable, because metastasis tumors could be in tissues or circulation far away from the primary tumors. One of ordinary skill in the art would have expected that a systemic non-specific immune response would occur from the intravenous administration of adjuvants, as taught by Bellnier et al, Sakurai et al, Malik et al, and Matsumoto et al, because adjuvants are well known in the art to produce or enhance non-specific immune response. It would have been obvious to administer the adjuvants or immune modulators either before or after PDT administration, because either way of administration would produce an enhanced immune response complementary to PDT treatment. It would have been obvious to administer proximate to the primary tumor site a photosensitizing agent such as Photofrin as taught by Bellnier et al, because it is notoriously well known in the art that cytotoxicity and tumor destruction from PDT are mediated by the interaction between the sensitizer and molecular oxygen within the treated tissue to generate cytotoxic singlet oxygen, and thus local administration of the sensitizer would enhance targeting or concentrating of the sensitizer to the primary tumor site. Concerning the concentration of DETOX, to determine optimum concentration of reactants is within the level of ordinary skill in the art. See In re Kronig, 190 USPQ 425. One of ordinary skill in the art would have a reasonable expectation of successful treating of primary and metastastic tumors, because PDT, besides killing neoplastic mass, is able to induce a strong specific anti-tumor immunity, as taught by

Canti et al, and because most adjuvants, such as TNF, IL-1, INF-gamma, monosaccharide-type adjuvant, Freud complete adjuvant, DETOX adjuvant, or G-CSF as taught by Bellnier et al, US 4,96,3354, Sakurai et al, Malik, A et al, Matsumoto, Y et al, and Kim et al, could be injected intravenously, and are complementary to the action of PDT, i.e. induction of antibody and T-cells responses against tumor antigens, as taught by Kim et al, and thus would kill metastatic tumors, as taught by Sakurai et al and Matsumoto et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

November 19, 2002

SUSAN UNGAR, PH.D
PRIMARY EXAMINER